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Enantioselective Catalysis Coupled with Stereodivergent Cyclization Strategies Enables Rapid Syntheses of (+)-Limaspermidine and (+)-Kopsihainanine A

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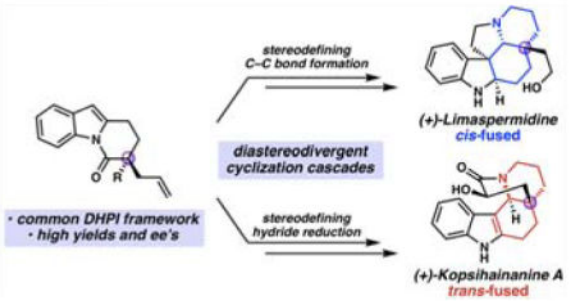
Abstract

Enantioselective Pd-catalyzed allylic alkylations of dihydropyrido[1,2-*a*]indolone (DHPI) substrates were used to construct the C20-quaternary stereocenters of multiple monoterpene indole alkaloids. Stereodivergent Pictet–Spengler and Bischler–Napieralski cyclization/reduction cascades furnish the *cis*- and *trans*-fused azadecalin subunits present in *Aspidosperma* and *Kopsia* alkaloids, respectively, en route to highly efficient syntheses of (+)-limaspermidine and (+)-kopsihainanine A.

Put a ring on it

Enantioselective Pd-catalyzed allylic alkylations of dihydropyrido[1,2-*a*]indolone (DHPI) substrates were combined with stereodivergent Pictet–Spengler and Bischler–Napieralski cyclizations to furnish the *cis*- and *trans*-fused azadecalin subunits present in *Aspidosperma* and *Kopsia* alkaloids, respectively, en route to highly efficient syntheses of (+)-limaspermidine and (+)-kopsihainanine A.



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This manuscript is dedicated to the late Professor R. B. Woodward on occasion of his 100th birthday.

Keywords

monoterpene indole alkaloids; allylic alkylation; asymmetric catalysis; stereodivergent cyclizations; total synthesis

Monoterpene indole alkaloids from the structurally related *Aspidosperma* and *Kopsia* families have been studied for more than half a century due to their intricate polycyclic structures and broad biological activities.[1,2] One significant structural difference between these families is the ring fusion geometry of the octa- or decahydroquinoline moiety contained within the polycyclic core. *Aspidosperma* alkaloids typically possess a *cis*-fused azadecalin motif (e.g., **1** and **2**, Figure 1).[3] Conversely, members of the *Kopsia* family often contain a *trans*-fused azadecalin substructure (e.g., **3** and **4**, Figure 1).[4]

We recently reported the enantioselective Pd-catalyzed allylic alkylation of dihydropyrido[1,2-*a*]indolone (DHPI) substrates (e.g., **5**, Scheme 1A).[5,6] The utility of the enantioenriched α-quaternary DHPI products (**6**) was illustrated through *regiodivergent* indole-iminium cyclization pathways to access multiple *Aspidosperma* alkaloids (**1**, **7**, and **8**). Given the high enantiopurities and rapid accessibility of these chiral building blocks, we sought to further investigate the versatility of the DHPI substrate class through *stereodivergent* indole-iminium cyclizations toward additional monoterpene indole alkaloid targets (Scheme 1B).

We envisioned that δ-lactam **9**, available in two steps from the α-quaternary Pd-catalyzed allylic alkylation product (**6**, Scheme 1A),[5a] could undergo hydride reduction and subsequent dehydration to deliver C2-tethered iminium **10** (Scheme 1B, blue path). A Pictet–Spengler-type cyclization could then occur, with the indole moiety approaching from the less hindered α-face, to yield tetracycle **11** bearing a *cis*-fused octahydroquinoline subunit. We anticipated that such an intermediate could be advanced to members of the *Aspidosperma* family of alkaloids, such as (+)-limaspermidine (**2**).[7] Alternatively, by reversing the order of these events (i.e., C–C formation *then* C–H formation), a Bischler–Napieralski cyclization could furnish tetracyclic iminium **12**, and the ensuing hydride reduction would proceed from the less hindered α-face to give the *trans*-fused octahydroquinoline subunit in tetracycle **13** (Scheme 1B, red path).[8] We expected that **13** could then be carried on in a total synthesis of (+)-kopsihainanine A (**3**) and additional *Kopsia* alkaloids.[6b,9]

Our synthesis of (+)-limaspermidine (**2**) began from unsubstituted DHPI **14**, which is available in multi-gram quantities in four steps from indole (Scheme 4).[5a] Straightforward C-acylation using allyl cyanoformate, followed by C-alkylation using (2-benzyloxy)ethyl iodide (**15**) delivered β-amidoester **16** in 80% yield over two steps. Exposure of **16** to a solution of $Pd_2(pmdba)_3$ (5 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**L1**, 12.5 mol %) in TBME at 60 °C delivered α-quaternary DHPI **17** in 82% yield and with 94% ee. Formal anti-Markovnikov hydroamination was accomplished using a hydrozirconation/amination protocol developed by Hartwig and co-workers.[10] Upon complete formation of the intermediate primary amine (**18**, not isolated), lithium aluminum hydride was added,

followed by careful quenching with acetic acid and water to promote the desired indole-iminium cyclization. This one-pot sequence delivered *cis*-fused tetracycle **19** in 60% yield. Chemoselective piperidine alkylation gave primary alcohol **20** in 83% yield (50% over two steps). Importantly, we found that tetracycle **19** could be advanced without purification to afford ethanolamine **20** in an improved 62% yield over the two steps. Pyrrolidine annulation, followed by subsequent hydride reduction yielded *O*-benzyl limaspermidine (**22**), which succumbed to debenzylation using excess BF_3•Et_2O in ethanethiol to provide (+)-limaspermidine (**2**) in 60% yield over the final three steps.[11]

Having successfully synthesized *cis*-fused azadecalin-containing (+)-limaspermidine (**2**), we turned our attention to an orthogonal synthesis of *trans*-fused (+)-kopsihainanine A (**3**). Beginning from the same tricyclic DHPI core (**14**), C-acylation followed by Michael addition with methyl acrylate furnished β-amidoester **23** in 92% yield over two steps (Scheme 3). Gratifyingly, subjecting **23** to our enantioselective Pd-catalyzed decarboxylative allylic alkylation conditions delivered α-quaternary DHPI **24** in 90% yield and 92% ee. We observed reduction of the methyl ester in **24** upon treatment with Schwartz's reagent, much to our disappointment, rendering the aforementioned hydrozirconation/amination protocol intractable in this setting. This setback notwithstanding, we implemented a Rh-catalyzed hydroboration to arrive at primary alcohol **25** in 87% yield.[12] Facile conversion of alcohol **25** to azide **26** occurred in 88% yield over two steps. A Staudinger reduction using polymer-bound triphenylphosphine proceeded with concomitant translactamization to afford δ-lactam **27** in 81% yield.[13]

The Bischler–Napieralski cyclization of **27** proceeded smoothly when employing a combination of triflic anhydride and 2-chloropyridine to provide *trans*-fused tetracycle **28** in 84% yield.[14] We next sought to effect a lactamization between the piperidine nitrogen and the pendant methyl ester. Numerous Lewis acids and Brønsted bases were examined, leading to the discovery that the guanidine base 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) could efficiently promote the desired cyclization to give strained pentacycle **29** in 65% yield.[15] The use of TBD for this type of lactamization provides a safer, more scalable alternative to existing procedures, which typically utilize highly pyrophoric trimethylaluminum.

Single crystal X-ray diffraction both confirmed the absolute configuration of **29**, and enabled the calculation of distortion geometries for the bridgehead lactam.[16,17] The high degree of pyramidalization at the bridgehead nitrogen (χ_N = 50.5°), along with the amide torsion angle (τ = 23.5°), explains the difficulty observed in forming this C–N bond (i.e., **28** ® **29**). Zhu and co-workers previously showed that exposure of (±)-**29** to lithium dimethylamide (LDMA) and bis(trimethylsilyl) peroxide in the presence of hexamethylphosphoramide (HMPA) as an additive could furnish (±)-kopsihainanine A (**3**) in 91% yield.[9b] As a result, we have completed a highly efficient enantioselective formal synthesis of (+)-kopsihainanine A (**3**) beginning from *N*-acyl indole **14**.

In conclusion, the combination of enantioselective Pd-catalyzed allylic alkylations of dihydropyrido[1,2-*a*]indolone (DHPI) substrates with *stereodivergent* indole-iminium cyclization strategies is a powerful tool for the synthesis of monoterpene indole alkaloids. The *Aspidosperma* family of alkaloids can be accessed by a stereodefining C–C bond

formation, highlighted herein by our synthesis of (+)-limaspermidine (**2**) in eight linear steps and in 25% overall yield from tricyclic DHPI **14**. Critically, a highly productive one-pot hydroamination/reduction/Pictet–Spenger sequence enabled the synthesis of the *cis*-fused decahydroquinoline moiety present in (+)-**2**. Furthermore, the *Kopsia* family of alkaloids can be accessed using a Bischler–Napieralski cyclization, followed by subsequent stereodefining hydride addition to furnish the opposite diastereomeric series. This capability was demonstrated through a nine-step synthesis (28% overall yield) of strained lactam **29**, thereby completing a formal synthesis of (+)-kopsihainanine A (**3**). Efforts to further exploit the synthetic utility conferred by the DHPI substrate class, particularly in the synthesis of more highly caged *Kopsia* alkaloids, will be reported in due course

Supplementary Material

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Acknowledgments

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15. Trimethylaluminum effected this lactamization in comparable yield, however we believe the use of TBD is both safer and more operationally simple. We did not observe the desired cyclization upon treatment with the amidine base DBU. Additionally, the binary solvent mixture of toluene/THF proved essential when using either TBD or $AlMe_3$.
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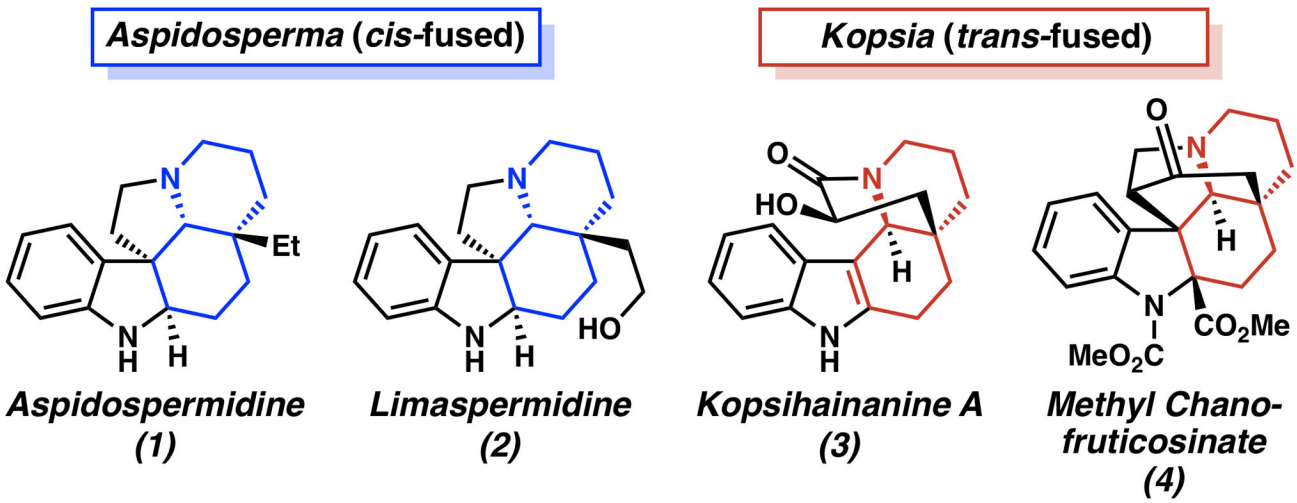
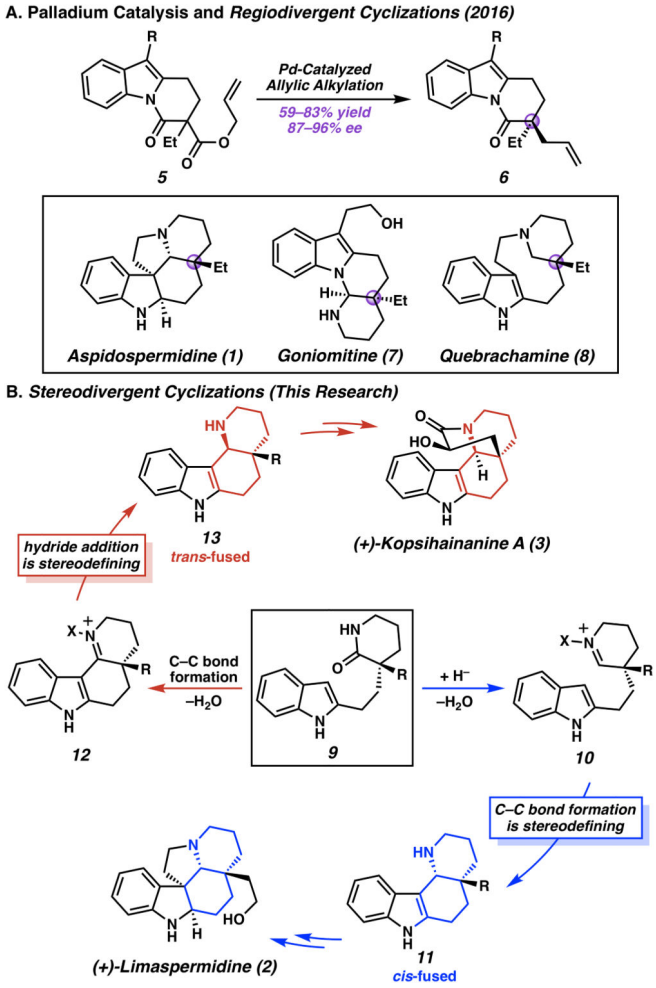
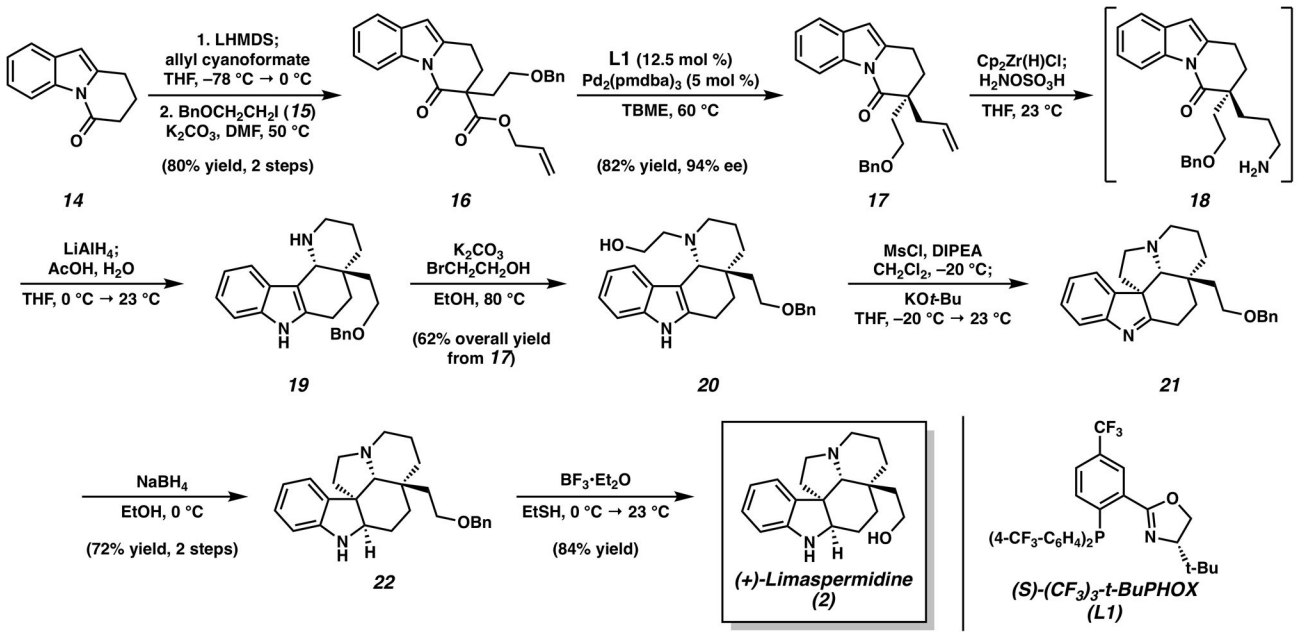


Figure 1.
Selected *Aspidosperma* and *Kopsia* alkaloids.

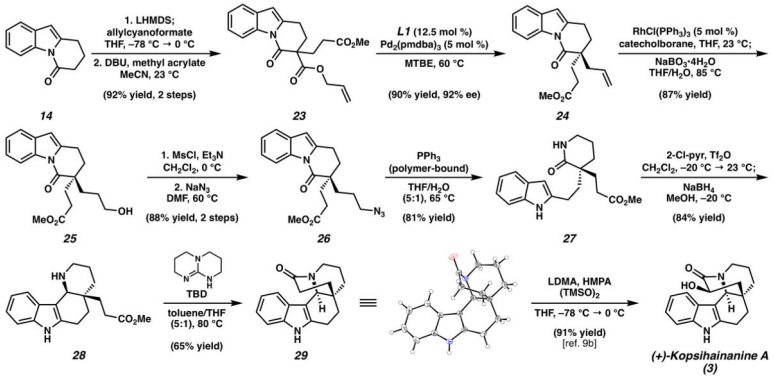


Scheme 1.

Enantioenriched α-Quaternary DHPIs as Precursors for Indole-Iminium Cyclizations.



Scheme 2.
Enantioselective Total Synthesis of (+)-Limaspermidine (**2**).



Scheme 3.

Enantioselective Formal Synthesis of (+)-Kopsihainanine A (**3**).